

**SECOND SUPPLEMENTAL  
DECLARATION**

**EXHIBIT A**

**MARCH 7, 2007  
OFFICE ACTION  
Paragraph 11, pages 7-9**

11. Applicant admits on page 9 that Examples 17-19 employ nucleic acids, but asserts that one skilled in the art reading the specification, which teaches that cells, i.e., stem cells (BMC's) possess equivalent activity to genes (nucleic acids) and other genetic material in forming a new artery (i.e., promote morphogenesis of an organ—artery), would be able to easily extrapolate the number on a weight basis of mononuclear cells required to obtain equivalent results. According to the method for extrapolation provided in the footnote to pages 10-11, 250  $\mu\text{g}$  of plasmid DNA (an amount described in Examples 17 and 18) divided by 40 pg, (asserted to be is the average DNA content of a cell; the species of cell is not disclosed) equals  $6.25 \times 10^6$ , and therefore the Examples 17 and 18 instruct the skilled artisan to use  $6.25 \times 10^6$  cells. This argument is not persuasive for several reasons. First, this method of converting plasmid DNA to cell equivalents is not included in the specification as filed. This is important because one of skill in the art would never think to attempt such an extrapolation. The unsound scientific basis for the conversion of  $\mu\text{g}$  of plasmid DNA to cellular equivalents would be obvious to anyone trained in molecular

biology. One basic assumption of the recited conversion is that the 40 pg of cellular DNA comprises the same gene dosage a purified plasmid DNA. Every molecule of the postulated plasmid DNA comprises a copy of the VEGF cDNA. In contrast, VEGF coding sequences would comprise but one of 30-40 thousand genes in genomic DNA (at the time of filing, it was widely believed that the human genome comprised 100,000 genes). Therefore, one of skill in the art at the time of filing would not expect plasmid DNA and genomic DNA to be comparable on a per weight basis. Applicant's argument seems to view the living cell as little more than a container for DNA. The expression of the recombinant cDNA would be under control of the limited number of enhancer and promoter elements in the plasmid, as opposed the native control elements with the genome. Therefore, even equivalent gene doses would not be expected to yield equivalent amounts of gene product with a plasmid as opposed to a cell. Applicant's argument seems to view the living cell as little more than a container for DNA. Delivery of the genes to a target as recombinant DNA as opposed to native genes within a living cell are technically different processes; there is no basis for using one to guide the other. For example, with DNA one is concerned with chemical stability, efficiency of uptake, stable retention, and subsequent expression of the injected molecule into target cells, whereas with cells separate issues of formation of effective attachment to ECM and neighboring cells, short- and long-term viability, and responses to environmental cues arise. As evidence, one need look no further than the US Patent classification system. Methods of *in vivo* treatments involving whole live cells as opposed to nucleic acids are separately classified: class 424 subclass 93.1 (cells); class 514, subclass 44 (polynucleotides). These separate classifications indicate a different status in the art such that it is well known that cell therapy and gene therapy are not obvious variants of one

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another. Therefore, contrary to Applicants assertion on page 9, the specification does not describe any dosage of cells to use to promote artery growth.